and using calculated likelihood ratios from the above expressions to create the array of likelihood ratios that are multiplied together with the pre pre-test odds factor to create the possible post-test outcome that indicates a possible disease and probability for the disease, according to the following mathematical expression:

(3) Pre-test odds x LR_1 x LR_2 x LR_3 x LR_4 ... x LR_n = Post-test odds, wherein

LR_{1-n} = positive and negative likelihood ratios calculated according to equations (1) and (2) above.

13. (cancelled)

14. (cancelled)

15. (cancelled)

REMARKS

This paper is filed in response to an office action dated August 24, 2005, relating to RCE application serial no. 09/698,787. Applicant presently has one claim pending.

In the last office action, the examiner rejected claim 12 under 35 U.S.C. Sec. 112, alleging that claim 12 added material not disclosed in the original specification. The above deletion of claimed subject matter (in the brackets in lines 35-37) makes the Sec. 112 rejection moot. Applicant reserves the right to traverse this rejection at a later point in time by way of a subsequent RCE filing or otherwise. It is respectfully submitted that a person skilled in the art will understand that the deleted subject matter is included in the original disclosure.

The examiner also rejected claim 12 under 35 U.S.C. Sec. 103. The Sec. 103 rejection is based on a three-reference combination of Iliff, Blinoska (or "Diagnostica"), and Sonis. The rejection of claims 13-15 is now moot in light of the above amendments.

As a threshold matter, Sonis apparently has a publication date of June 1999. Applicant's application claims priority to a provisional patent application filed in October 1999. For the purpose of the record, applicant is not conceding that Sonis is prior art. Even if it is, applicant respectfully submits that claim 12 is allowable over the combination of the three references cited by the examiner, and the other known prior art of record, for the following reasons.

In earlier papers applicant discussed applicant's use of Bayesian theory to predict the probability of disease. Applicant also discussed the differences between purely "rules based" systems vs. "evidenced based" systems – the latter being the best way to characterize the difference between applicant's system and the prior art (like Iliff), in a general way. Applicant has also explained that the subject matter of applicant's system enables the prediction of multiple outcomes (e.g., post-test odds for a multiple number of diseases, all done at the same time).

With respect to the claim amendments submitted above, the examiner first interpreted Iliff as teaching a web-based system that generates a plurality of possible post-test outcomes (i.e., predicted diseases). However, the examiner acknowledged that Iliff "*fails* to explicitly disclose the common template being used to generate a matrix...and each possible post-test outcome of the plurality of possible post-test outcomes...being generated from an array of [independent] mathematical factors that are based on patient symptoms and information...." (8/24/2005 Office Action, p.6) (Emphasis added.)

With respect to what Iliff fails to teach relative to the claimed invention, the examiner then held that what Iliff lacks is nevertheless well-known in the art, as evidenced by Diagnostica (Office Action, p.6-7). Finally, while Diagnostica does not teach the use of likelihood ratios, the examiner held that Sonis discloses likelihood ratios and then combined Sonis with Diagnostica

(Office Action, p.8) – the end result being a three-reference combination (Iliff, Diagostica and Sonis) to reject the claims.

First, applicant respectfully submits that Diagnostica cannot be combined with Iliff to produce the claimed invention. To combine references, the combination must be suggested by looking only at the references themselves, and not by using the patent application claim as a guide to make the combination. This, of course, is a fundamental rule that the USPTO follows in order to avoid the mistaken combination of references on the basis of hindsight. Use of hindsight to combine references is grounds for appeal to the Board of Appeals and the Federal Circuit. It is respectfully submitted that it appears the examiner may be erring by using the claimed subject matter as a guide for combining references.

When Iliff makes no teaching of the claimed template or array defined in claim 12, as the examiner has acknowledged, then it is not appropriate to presume that the techniques described in the Diagnostica paper can be lifted and input into Iliff like an interchangeable subroutine. The Diagnostica paper employs different methodology relative to the branch-tree or rules-based system that Iliff uses. As such, it is not interchangeable – which means there would be no suggestion to combine these two references. The mathematical techniques described in Diagnostica will not fit into Iliff – at least not without reworking Iliff in a way that is simply not suggested by either reference. If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959).

Moreover, Applicant has now amended the language of claim 12 to clarify that the claimed "array" is more than a mere series of factors multiplied together (*see* lines 24-34). The

claim is now more specific in that it calls for a pre-test odds number that is multiplied by a plurality or series of *likelihood ratios* (to produce post-test results). *See, e.g.,* specification page 20. Iliff does not describe anything like that; nor does the Diagnostica paper describe anything like that; even if it is proper to combine these two references. Moreover, Sonis does not describe or suggest the limitation.

Next, with respect to the combination of Sonis with Diagnostica, the specific mathematical techniques described in each reference teach away from their combination. Sonis admittedly discloses how to calculate *a single* likelihood ratio and teaches what a likelihood ratio means in terms of probability (*see* Sonis, p. 434). However, Diagnostica teaches a mathematical calculation that is different – that is, density distribution calculations. One cannot substitute a likelihood ratio calculation, as per what Sonis describes, into the density distribution calculations that Diagnostica describes, simply because both references may mention the term "Bayesian."

There are different kinds of statistical techniques that are not interchangeable, even though all may be Bayesian, in general terms. In this instance, while both Diagnostica and Sonis fall under the rubric of "Bayesian," one cannot use the word "Bayesian" (which is mentioned in both references) as the reason for holding that a density distribution calculation is interchangeable with a likelihood ratio calculation.

In addition to the above, the amendments in lines 35-55 of claim 12 specify a very specific form of user-created template for generating a matrix of likelihood ratios – which is not shown in *any* reference of record. The mathematical expressions in the claim are very specific to the template form that is defined in the claim, and described in the specification (applicant points to the applicable specification parts below), and provide the means for calculating a likelihood ratio for each "cell" (*see* Fig. 11 of the specification) of the claimed matrix.

Sonis deserves special mention at this point because it discloses how one can multiply a single likelihood ratio with a pre-test odds number to produce a post-test odds number (*see* Sonis, p. 435). Sonis does not, however, teach the calculation and multiplication of an *array* of likelihood ratios in a string or series – which is first set forth conceptually in lines 24-34 of claim 12 and then mathematically in lines 58-59. This form of likelihood ratio multiplication borne out of a matrix of cell values has not been used in the relevant prior art (medical diagnostics), at least to applicant's knowledge. *See*, specification page 20.

The latter point is significant relative to what the prior art references disclose. As stated above, the mathematical expressions in the claim are very specific to the template form that is described in the specification. One clearly distinguishing feature of the claim, relative to the prior art cited by the examiner, is that a likelihood ratio is calculated *for each* "cell." This is an important difference relative to how likelihood ratios are calculated in the prior art of record.

The examiner's attention is directed to page 15 of the specification (third paragraph) which states, "Likelihood ratios (preference value) are computed for each criterion value." The criterion value is "X," as is clear from the specification (which corresponds to the "X" value in lines 47-53 of claim 12). In other words, "X" is defined in the claim as a "mathematical cell value." The examiner's attention is likewise directed to the sixth block down on the block diagram or flow chart illustrated on Fig. 11 of the specification. This block illustrates the same equation in flow chart form. Claim 12 specifically requires that a likelihood ratio be calculated for *each* cell value (or "X") in the claimed matrix. This is not what Sonis does.

The examiner will appreciate that the mathematical nomenclature used in claim 12 adopts the symbols used in the flow chart on Fig. 11. While the symbols are different, in some instances, the mathematics illustrated in Fig. 11 is *identical* to the mathematics described on page

15 of the specification, along with the matrix and cell values illustrated on page 15. Once again, what is particularly relevant, mathematically, is that claim 12 calls for calculation of a likelihood ratio for each cell that is based on "M" (see claim 12, line 50). "M" is the sum of *all* cell values across all rows and columns in the matrix.

While applicant has chosen to use "M" as the nomenclature in the claim (which is what the flow chart on specification Fig. 11 uses), as the examiner will appreciate, "M" is the same thing as "μ" on specification page 15. Applicant intends to correct nomenclature by either filing a substitute specification, with the examiner's permission, or in a subsequent RCE filing.

Conceptually, if the examiner refers to the "classic" 2 X 2 matrix that is described in Sonis (which applicant also identified as the "classic" example in the specification), that matrix sets forth four cell values. According to Sonis, these four cell values are used to create *only one* likelihood ratio for the entire 2 X 2 Sonis matrix. In comparison, the mathematics that is set forth in claim 12 results in a likelihood ratio calculation *for each cell* in the matrix – which means that *four* likelihood ratios would result from a 2 X 2 matrix (in actuality, the number is *eight* likelihood ratios, according to claim 12, because applicant calculates a "positive" and "negative" likelihood ratio for each cell).

Thus, according to claim 12, if the matrix is 2 X 3, then it creates six cells (and twelve likelihood ratios), and so on, as the size of the matrix increases. Once again, the value of each likelihood ratio calculation is mathematically related to "M" (the same thing as "μ") – which is the sum of *all* cell values ("X") across all rows and columns in the matrix – an ever changing number that is related to individual cell values *and size of the matrix as it expands both in the numbers of rows and columns in the matrix.*

This type of template, or matrix, as defined in claim 12, permits the scalability that applicant described in earlier papers. That is, post-test odds and/or post-test probability of a disease is calculated by multiplying a pre-test odds number by a *series* of likelihood ratios. The series of likelihood ratios is produced from the matrix calculation – with the matrix being expandable in two dimensions, infinitely, if desired.

By way of further explanation, in actual use, the number of columns in the matrix correspond to statistically-accrued variables that may be taken from medical test results, historical patient history data, demographic data or, literally, any number of statistically relevant factors that may indicate the presence or absence of a disease. Likewise, the numbers of rows in the matrix will correspond to each possible outcome (or disease probability) that is entered into the matrix (once again, post-test odds for each outcome is calculated by multiplying the array of cell values (i.e., calculated likelihood ratios) in the matrix row that corresponds to the outcome). *See, e.g.,* matrix on specification page 15.

Moreover, the user may make changes to template or matrix scale at any time. In this respect, the examiner will note that applicant is now claiming a user-defined template, or matrix, having a number of rows and columns "that is greater than 2 X 2" (line 40), which is consistent with this concept and describes something different from the "classic" 2 X 2 matrix described in Sonis.

One of the advantages provided by the claimed technique of using larger matrices is that it allows new pieces of relevant information to be added to diagnostic probabilities that go beyond a single medical test. In other words, if the examiner revisits Sonis, the examiner will note that Sonis calculates a single likelihood ratio based on a medical test (the classic example). How likelihood ratios work in this context was explained earlier – as an example, just because a

professional athlete tests "positive" for steroids, the test is not 100% accurate. There will always be a certain percentage of athletes who test positive for steroids but have never used them. Likewise, some athletes who use steroids sometimes test "negative," anyhow. Likelihood ratios are an aspect of Bayesian theory that generates a probability factor taking into account the reliability (or unreliability) of test results.

Applicant's invention partially incorporates this concept (*see* claim 12, lines 41-43: "more than two criterion including positive and negative test results"). More importantly, however, the template system claimed by applicant allows *other* factors to be included in the calculation of further likelihood ratios - that are not necessarily related to test results. As an example (hypothetical), a steroid test may be more accurate for a female athlete than a male athlete. That piece of information can be added to the matrix as part of the mathematical likelihood ratio calculations set forth in claim 12. As another example (hypothetical), steroid tests may be affected by whether the athlete eats red meat or is a vegetarian. These additional pieces of information can also be added to the matrix (by adding columns) to expand over and beyond the classic calculation of an individual likelihood ratio based solely on a test result (Sonis) – thus creating a series of likelihood ratios multiplied in an array in each row of the matrix to create a post-test odds number for each row.

To explain scalability further in terms of rows (or multiple outcomes), the above example seems to suggest a technique for predicting the probability of steroid use – which is a single predicted outcome (i.e., positive or negative test) and, hence, "two" rows in the matrix – one for steroid use and one for non-steroid use. What the applicant means by scalability is that the tests and other data used in connection with testing an athlete for steroids can generate other outcomes as well. As a hypothetical example, an athlete who regularly uses steroids may be more

susceptible to other ailments (heart disease, certain forms of cancer, etc.). Each one of these other potential ailments can be included as other potential outcomes in the claimed template, or matrix, with another row of likelihood ratios that creates a post-test odds number for the specific ailment. This is precisely what the applicant means when applicant uses the term "scalability" in this paper and in the remarks in previous papers – the template or matrix form claimed by the applicant, along with the mathematical technique of calculating a likelihood ratio for each cell in the matrix (which is calculated, in part, from the values of *all* cell values in the matrix), allows columns and rows to be added or subtracted easily. These additions or subtractions correspond to the addition of new pieces of relevant data or the discard of data that is later determined to be irrelevant or untrustworthy (columns), or the addition or subtraction of other predicted diseases (rows) from the matrix.

These examples are given for the purpose of illustrating that the claimed invention provides a way to expand the accuracy of likelihood ratio calculations based on the accumulation of new statistical data, regardless of whether it is based on existing medical tests, new medical tests that may later prove to be more accurate, or based on other things like pure observational data (i.e., demographics, culture, environmental considerations, etc.). Applicant's latest amendment to claim 12 includes this additional concept (*see* claim 12, lines 41-43: "and further including other criteria that are independent of test results") – which is not part of Sonis's teachings or the other prior art of record.

The utility of the technique claimed in the present case, which was mentioned in earlier paper, is that changes are very easy to implement. In a rules-based programmable system, like the one disclosed in Iliff, adding new tests or discarding old ones, means rewriting code. That is not true with the present invention.

Once again, according to claim 12, each calculation that is based on one of the available criteria (i.e., test data, observational data, etc.) results in a single likelihood ratio calculation for each cell in the claimed matrix calculation set forth in claim 12. *All* of the likelihood ratios that are calculated can then be tied together by multiplying them in series in an array (one array for each matrix row) – the number of likelihood ratios in the array also scaling toward infinity as the likelihood ratio-calculation matrix expands by column numbers. *See, e.g.,* specification page 20. This technique serves to adjust the pre-test number upward or downward (or not at all) depending on the value of each likelihood ratio calculated in the series.

According to the way applicant defines it, a "positive" likelihood ratio, as claimed, denotes the association between a variable and a specific outcome. A "negative" likelihood ratio denotes the *lack* of association between a variable and a specific outcome. For example, a positive likelihood ratio between regular exercise and heart disease would have a value "less than 1" which means those who exercise have reduced instances of heart disease. A negative likelihood ratio between regular exercise and heart disease would have a value "greater than 1" which means that those who *do not* exercise (the negative association) have increased instances of heart disease. The type of user-enabled template that is claimed in lines 37 - 43 provides the means for creating each type of likelihood ratio (e.g., as per applicant's disclosure on specification pp. 13-16). Once again, the examiner will further appreciate that the applicant is now specifically claiming both "positive" and "negative" likelihood ratios as part of the array (claim 12, lines 47-48) – a feature that is not described in any of the references cited, as far as applicant can determine.

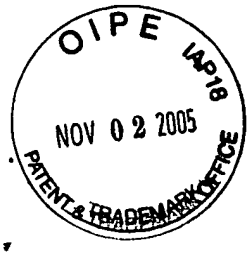
In summary, if the examiner compares the mathematical models and their computational sequences used in Iliff, Diagnostica, and Sonis to the mathematical expressions set forth in claim

12, the only reasonable conclusion is that the mathematics is different. None of the references cited by the examiner disclose the type of array claimed above; none disclose the type of user-enabled template that is claimed above (which serves to generate positive and negative likelihood ratio calculations for each cell of a matrix); none disclose the calculation of likelihood ratios from each cell in a matrix; and none of the references disclose taking these likelihood ratio calculations and multiplying them together against a pre-test odds number to create a post-test odds number. Even if it is reasonable to presume that Iliff and Diagnositica and Sonis could be combined together, that combination still fails to teach what is claimed.

With respect to support in the existing specification for the claimed subject matter, the subject matter of lines 35-55 is described in Fig. 11 of the specification, in particular, and in Figs. 12-14, more generally, and in the specification text at pages 13-16. The array multiplication discussed above is described on specification page 20, along with a higher-level discussion concerning how this type of likelihood ratio technique can be applied in other fields.

For the foregoing reasons, applicant respectfully requests that the examiner give an indication that the claim has allowable subject matter. Applicant acknowledges the examiner's entry of a requirement that the specification be revised if applicant continues to prosecute the application. Applicant respectfully requests that this requirement be held in abeyance until the examiner gives an indication of allowable subject matter. At that time, applicant will submit a substitute specification by way of an RCE filing.

Finally, applicant wishes to thank the examiner for her thorough analysis and examination of the prior art in the office action. If the examiner has any questions concerning the operation of the invention or the information set forth in the specification, she may contact applicant's attorney directly.



Respectfully submitted,

VICTOR LEVY

By: Bruce C Kaser

Bruce A. Kaser
Registration No. 31,531
VANTAGE LAW PLLC
355 NW Gilman Blvd
Suite 203
Issaquah, WA 98027
Telephone: (425) 391-8741

I, Bruce A. Kaser, hereby certify that this document and its attachments are being deposited with the U.S. Postal Service as First Class Mail, postage prepaid, in an envelope addressed to Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 31st day of October, 2005.

Bruce C Kaser
Name (signature)